TABLE 25
Baseline-entry characteristics (interim report of 40 patients)

Parameter		# patients (%)
Age (years)	Median	59
	Range	23 - 80
	> 65 years	11 (28%)
Sex	Male	27 (68%)
	Female	13 (32%)
Race	Caucasian	28 (72%)
	African American	10 (25%)
	Other	1 (3%)
CTCL Stage	≤ II a	23 (58%)
	≥ II b	13 (32%)
# Prior therapies	≤ 3	27 (68%)
	2 4	13 (32%)

Eight patients failed to complete all planned therapy. There were 21 reports of serious adverse events in 8 of the 40 patients. Eight (20%) patients were withdrawn from the study due to adverse events. Toxicities observed in this trial are similar to those observed in protocols 92-04-01 and 93-04- 10; the adverse event profile is summarized in tables contained in the Integrated Summary of Safety.

V. IMMUNOHISTOCHEMISTRY ASSAY TO DETECT IL-2 RECEPTOR EXPRESSION IN CLINICAL STUDIES

Demonstration of IL-2R expression by ≥ 20% of the cells in either tissue biopsy or circulating cells was a requirement for enrollment into the $DAB_{389}IL\text{-}2$ clinical studies. For Protocol 92-04-01, expression of the p55 subunit (CD25) and/or the p75 subunit (CD1 22 detected by the mikβ-1 antibody) of the IL-2 receptor was required; for all subsequent studies. expression of p55 subunit (CD25) of the IL-2 receptor was required. The assessment of CD25 expression was based upon the percentage of cells in the field rather than the percentage of tumor cells. because of the difficulty in accurate identification of tumor cells in biopsy or peripheral blood specimens. The selection of ≥20% of the cells expressing the CD25 (or in the case of 92-04-01. CD1 22as evidence of IL-2R expression was justified (by the sponsor)as follows: "The percentage of cells expressing IL-2R was set at a high level (≥ 20%) on the assumption that this level of IL-2R expression could not attributed to activated T cells alone and therefore must represent IL-2 R expression by malignant cells."

Skin biopsy samples were sent to a central pathology laboratory (. [redacted] Formalin-fixed and paraffin-embedded sections were to confirm the underlying diagnosis (CTCL, HD, or NHL) and frozen sections

were used for immunohistochemical analysis. Frozen tissue samples underwent staining with a ——————— technique. The enzyme was localized using the ——————— with ——————— and the preparation was counter-stained with ——————— All specimens were assigned an intensity staining grade (Table26); only patients assigned 2+ or 3+ staining were eligible for study.

TABLE 26
Immunohistochemistry Scoring System

Grade	% Cells Staining for Marker
0	no staining above background
1	< 20%
2	20% to 50%
3	> 50%
4	Indeterminate

In Protocol 92-04-o 1, there were 93 CTCL patients with evaluable tumor specimens; of these, 58 patients' tumors were IL-2R positive (2+ to 3+ expression), 8 were indeterminate, and 27 had no detectable IL-2R expression. There were 24 patients with HD screened, of whom 20 (83%) had IL-2R positive tumors and 75 patients with NHL who were screened, of whom 3 1 (4 1%) had IL-2R positive tumors.

Protocols 93-04- 10, 93-04- 11, and 93-04- 14 enrolled only subjects with a diagnosis of CTCL. All except 93-04-14 required IL-2R (CD25) expression [the exception was for patients who had previously received and responded to DAB_{389}IL-2 in 93-04-10 or 93-04-l 1. and were enrolled in 93-04-14 for retreatment]. There were 345 skin biopsy samples obtained from 3 10 patients that were screened for entry. Samples were assessed for CD25. CD20, CD22. CD4, CD8 and CD7 by immunobistochemistry. The CTCL population was postulated to be CD25 +, CD4 or CD8 +, CD20-, CD22-, CD7-. Of the 3 10 patients screened for entry, >80% of the cases exhibited CD3, CD4, and CD5 expression. The p55 subunit (CD25) was present in 58% (201 of 345 specimens)., Of the 201, 84% had a staining score of 2 and 16% had a score of 3+.

VI. INTEGRATED SUMMARY OF EFFICACY

A total of 257 patients with CTCL or lymphoma baseline entry have been enrolled in four studies using DAB_{389}IL-2. Pertinent characteristics of the patients with CTCL enrolled in studies of DAB_{389}IL-2 are summarized in Table 27.

TABLE 27: Baseline Characteristics By Protocol

Characteristic	Protocol			
	93-04-10	92-04-01	93-04-11	93-04-14
Characteristics	**N = 71**	**N = 73**	**N = 73**	**N = 40**
Gender				
Male	37 (52%)	44 (60 %)	39 (53%)	27 (68%)
Age, years				
≥ 65	35 (49%)		21 (29%)	11 (28%)
Median	64.0		55	59
Range	26 – 90	16 - 81	23 – 84	23 - 80
Race				
Caucasian	53 (75%)	32 (44%)	54 (74%)	29 (73%)
African American	12 (17%)	7 (10%)	17 (23%)	10 (25%)
Hispanic	6 (9%)	9 (12 %)		
Other /Unk.		25 (34 %)	2 (3%)	1 (3%)
CTCL Biological Diagnosis				
MycosisFungoides	54 (76%)	35 (100%)	N/A	N/A
Sézary Syndrome*	17 (24%)		N/A	N/A
CTCL Stage				
≤ II a	**26 (37%)**	12 of35 (34%)	**51** (70%)	**23 (58%)**
≥ II b	**45 (63%)**	**23** of35 (66%)	22 (30%)	**13 (33%)**
Prior Tx CTCL				
o - 1	**3 (4%)**	**7** of 35 (20%)	**71 (97%)**	**27 (68%)**
2 - 3	**6 (9%)**	11 of 35 (31%)		
≥ 4	62 (87%)	17 of 35 (49%)	2 (3%)	13 (33%)

The population enrolled in the efficacy studies (92-04-o 1 and 93-04- 10) differs from the ongoing studies (93-04-l 1 and 93-04014). In the efficacy studies, the patient population was older (49% vs. 28-29% of patients ≥65 years) and patients had more advanced stage disease (two-thirds of patients had ≥ stage IIb as compared to 1/3 of the patients in the ongoing studies). In addition, patients in efficacy trials were more extensively pretreated, 74% received ≥ 4 prior treatment regimens, whereas the majority of patients (87%) in the su7bsequent trials have received ≤-3 prior treatment regimens.

A. Primary and exploratory efficacy analyses for Protocols 93-04-l 0 & 92-04-o 1

Protocol 93-04-I 0

The primary assessment of response in protocol 93-04- 10 (and in the ongoing studies 93-04- 11 and 93-04-14) is based upon the determination of an independent review committee (DERC). The DERC identified fewer responders in Protocol 93-04-10 than did the clinical investigators. The DERC identified 21 of 71 patients (30%) with the objective clinical responses. This included three patients with clinical and pathological complete responses (CR), four patients with clinical complete responses (CCR). and 14 patients with partial responses. The finding of a lower response rate by an independent third party review is common. however the differences in response rates reported by DERC and the investigators (48% vs. 30%) are rather large. It is unclear whether the differences may also be due to the difficulty in assessing disease status in CTCL.

Pooled Data from 92-04-01 and 93-04-I 0

The assessment of responseby the DERC was conducted for only one of the two trials. For comparison, across the two studies (92-04-o 1 and 93-04-10), the investigator-assessments for complete and partial response are provided in the next several tables. The complete response rates are the same in the two trials, while the partial response rate, as determined by the clinical investigators, is lower in Protocol 92-04-01 than in 93-04-10.

TABLE 28
Investigator-Assessed Response By Protocol and Pooled

	93-04-10 (n = 71)	92-04-01 (n = 35)	Total (n = 106)
CR	13 % (9/71)	14 % (5/35)	13 % (14/106)
PR	35 %(25/71)	23 % (8/35)	31 % (31/106)
ORR	48 % (34/71)	37 % (13/35)	44 % (47/106)

The sponsor incorporated a dichotomous stratification (≤ Stage IIa vs. ≥ Stage IIb) in the randomization plan for Protocol 93-04-l 0. In pooling the study results, responses were observed in 22 of 37 (59%) patients with Stage Ia-IIa disease; the response rates for patients with ≤ IIa disease was very consistent between the two studies. Twenty-five responses were reported among 69 patients with ≥ IIb disease, for an overall response rate of 36%. The response rate for late stage disease less consistent between the two studies. The ORR in late stage patients was higher (42% vs. 25%) in Protocol 93-04-10 which enrolled approximately twice as many late stage patients as Protocol 92-04-01. There was a significantly higher response rate for patients with ≤ Stage IIa disease as compared to those with ≥ Stage IIb (59% vs. 36%. p=0.03) in the pooled population.

TABLE 29
investigator Assessed Response Rates by Early vs. Late Stage Disease

Stage of Disease	Response Rate by Protocol		Overall Response Rate
	93-04-10	92-04-01	
Early Disease (≤ Stage II a)	58 % (I 5/26)	64 % (7/11)	59 % (22/37)
Late Disease (2 Stage II b)	42 % (19/45)	25 % (6 124)	36 % (25/69)

There was no evidence of a dose-response relationship in either Protocol 92-04-01 or Protocol 93-04-10. There was no significant difference in overall response rates between the "low" (6-l 5 µg/kg/d) vs. "high" (18-3 1 µg/kg/d) dose ranges in the pooled data sets (Table30).

TABLE 30

Pooled Investigator-Assessed Response Rates by Dose Range (Low vs. High)

Response Rate	Dose Range	
	6-15 µg/kg/d	18-31 µg/kg/d
CR	12% (6/49)	15% (9/57)
PR	28% (14/49)	32% (19/57)
ORR	40% (20/49)	47% (28/57)

B Efficacy analyses in supportive studies

Protocol 93-04-I 1

The study remains blinded as to treatment arm. Among the 70 patients with sufficient follow-up, the clinical investigators have reported 18 patients with partial responses (ORR and PR 29%). These objective tumor responses have not yet been assessed or verified by the DERC at the time of this submission.

Protocol 92-04-01 (Non-CTCL)

There were 38 patients with diseases other than CTCL enrolled in this study. No objective tumor responses were reported among the 21 patients with Hodgkin's disease. There were 3 objective responses (1 CR and 2 PR) reported by investigators among 17 patients with NHL. There were two responses among 7 patients with low-grade histology, one response among 6 patients with intermediate grade histology and no responses reported in four patients with high-grade histology. The reported response durations were 2, 9, and 20+ months. These responses were reported by the clinical investigators and were not assessed or verified by an independent review committee.

DAB- IL-2 Studies

DAB-, IL-2 Phase I/II studies: Thirty-six patients with CTCL enrolled in these studies. Investigators reported 6 patients with objective clinical responses for an overall response rate of 17%.

VII. Integrated Summary of Safety

A. Studies in Malignancies

Data from 256 patients with lymphoma enrolled in $DAB_{389}IL\text{-}2$ studies were provided in the application. There were 4 studies enrolling 2 18 patients with CTCL; one of these studies also enrolled 38 patients with NHL and HD. A summary of the safety information in patients with non-malignant or AIDS-related malignancies enrolled in $DAB_{389}IL\text{-}2$ studies will be integrated and reported in the following section (VII B).

2 18 patients with cutaneous T-cell lymphoma

- 35 patients in Protocol 92-04-01
- 71 patients in Protocol 93-04-l 0 [8]
- 73 patients in Protocol 93-04-l 1 (2: 1 randomization to $DAB_{389}IL\text{-}2$ vs. placebo)
- 40 patients in Protocol 93-04-14

38 patients with Hodgkin's Disease & Non-Hodgkin's Lymphoma (Protocol 92-04-01)

(1) GENERAL

All patients in Protocols 92-04-o 1 and 93-04- 10 reported one or more adverse events. Approximately 80% of the adverse events were Grade 1 or 2 in severity and 15% were Grade 3 in severity. More than half of the adverse events was reported during the first two cycles of treatment. There are two potential reasons that this may have occurred. First, the rate of early discontinuation from treatment was high (median number of treatment cycles was 2) in Protocol 92-04-01, which may have resulted in a lower incidence of adverse events in later treatment cycles due to early termination of patients at higher risk for toxicity. This was not observed in Protocol 93-04-l 0, where the median number of treatment cycles administered in both the low and high dose arms was 6 cycles. Secondly, the generation of an anti-DABJL-2 immune response was observed in nearly all patients after the second cycle, with rapid clearance of drug product; this may also have contributed to the lower incidence of toxicity in later cycles. One additional factor, which may have altered the incidence of infusion-related adverse events, was the use of premedication to prevent infusion reactions. which was common. The studies were not designed to determine the effectiveness of such interventions in preventing toxicity; the results of retrospective analyses looking at the potential effectiveness of premedication do not indicate that it was beneficial.

Several clinically distinct syndromes of toxicity were observed during the clinical trials. These included an acute flu-like[9] syndrome, acute hypersensitivity-type reactions. vascular leak syndrome and gastrointestinal (Gl) symptoms (nausea, vomiting, and diarrhea). Fever and/or chills (81%). asthenia (66%). headache (26%). myalgias (18%). and arthralgias (8%) characterized the acute flu-like syndrome. which developed within hours of the first several doses.

Acute hypersensitivity-like reactions

Acute hypersensitivity-like reactions were experienced by 98 of the 143 patients in the efficacy trials, and were characterized by one or more of the following: hypotension (50%[49/98]). back pain (30%), rash (25%), dyspnea (28%), chest pain or tightness (24%) and tachycardia (12%). Other less frequent symptoms include dysphagia or laryngismus (5%). syncope (3%). allergic

(i)

8 Patient 2119 was excluded by the sponsor from the safety database because this subject was ineligible for the protocol (had received external beam radiotherapy and chemotherapy in the immediate pre-study period); adverse event information on this patient is excluded from the tables but included in descriptions of serious adverse events in this review.

9 Acute flu-like syndrome includes fever. chill and/or rigors, arthralgias. myalgias, headache. malaise. and asthenia

reaction (1 %) and anaphylaxis (1 %). Hypersensitivity reactions were most common during the first two cycles and were managed by a decrease in the rate of infusion alone or with additional medical intervention. Medical interventions included intravenous fluid resuscitation (administered for 9 events in 8 patients, with grade 2-3 hypotension), antihistamines alone (1 patient), antihistamines plus corticosteroids (1 patients), antihistamines, corticosteroids, and supplemental oxygen (1 patient); and vasopressors/epinephrine (1 patient). Two patients in the efficacy studies (1 % [2/1 43]) and 5 (2%) of the 256 patients enrolled in the 4 clinical trials in lymphoma discontinued treatment due to hypersensitivity reactions.

Vascular Leak Syndrome (VLS)

At the request of FDA, the sponsor conducted a retrospective review of the patients in the two efficacy studies to evaluate the incidence of this syndrome. Physician-consultants reviewed the database and identified all patients meeting the definition of VLS (at least two of the following: hypotension, edema, and grade 2-4 hypoalbuminemia). Based upon this review, there were 46 episodes of VLS identified in 38 of the 143 patients (27%) enrolled in Protocols 93-04-l 0 and 92-04-01. Hypoalbuminemia was the most frequent manifestation of VLS, identified in 34 of the 38 (89%) patients. Hypoalbuminemia was generally delayed in onset (days 5 - 13 of treatment cycle). Twenty-three of the 34 patients (68%) had grade 2 hypoalbuminemia and 11 (32%) had grade 3-4 hypoalbuminemia. Edema was identified as a component of VLS in 30 of the 38 (79%) patients and hypotension as a component of VLS in 21 of the 38 (55%) patients. There were 5 reports of pulmonary edema in the two studies; all 5 occurred in patients with VLS.

Six percent (8/1 43 patients) of patients in the efficacy studies and 21% (8/38) of those with VLS were hospitalized for the management of VLS. Based upon a review of the records. the management of VLS consisted of diuretic therapy in 15 of 46 events (33%); intravenous fluids in 12 of 46 events (26%); intravenous albumin in 4 of 46 events (9%);supplemental oxygen for treatment of hypoxemia in 4/46 events (9%); and vasopressors in one event. No patient received corticosteroids for treatment of VLS.

Characteristics of VLS by component, incidence, and severity

Component of VLS	# Pts	Severity Grade (by # of Pts)		
		1	2	3 - 4
Hypoalbuminemia	34	0	23	11
Edema	29.	5	11	13
Hypotension	21.	4	12	5

Prophylactic medication usage

Use of prophylactic medications to prevent infusion-related toxicities (flu-like symptoms and hypersensitivity-type reactions) was common. These included acetaminophen alone (n= 19) or in combination with diphenhydramine (n=77), antihistamines, H_1 and/or H_2 blockers, (n=85), non-

steroidal anti-inflammatory drugs (NSAIDs) in 85 patients, and corticosteroids (n=5). The studies were not adequatelydesigned to address whether premedication may ameliorate DAB_{386}-IL-2 toxicity, in that both protocols specifically prohibited prophylactic medication to prevent symptoms on the first exposure and use of premedication after that point was not controlled or standardized. The results of retrospective analyses evaluating the association between symptoms and premedication use suggest that antihistamines and NSAIDs or acetaminophen were associated with reductions in infusion-related symptoms, however the results of these comparisons, which were statistically significant, were not adjusted for multiplicity. Such observations should be confirmed in an appropriately designed intervention study to determine the clinical utility of premedication use.

Table 31A: Retrospective analysis of the association between prophylactic medications and the incidence of hypersensitivity reactions (by cycle)

	Antihistamine n=1447	No Antihistamine n=1468
# cycles w/symptoms	260 (18%)	324 (22%)
# cycles w/o symptoms	1187 (82%)	1144 (78%)
	NSAID/Acet n=1407	**No NSAID/Acet n=1508**
# cycles w/symptoms	241 (17%)	343 (23%)
# cycles w/o symptoms	1166 (83%)	1165 (77%)

Table 31B: Retrospective analysis of the association between prophylactic anti-emetic use and the incidence of nausea/emesis (by cycle)

	Anti-emetic use (n=168)	No anti-emetics (n=2747)
# cycles with nausea/emesis	15 (9%)	259 (9%)
# cycles without nausea/emesis	153 (91%)	215 (9%)

Table 31C: Retrospective analysis of the association between prophylactic anti-emetic use and the incidence of constitutional symptoms (by cycle)

# cycles w/symptoms	269 (22%)	718 (43%)
# cycles w/o symptoms	966 (78%)	962 (57%)
# cycles w/fever or chills	178 (13%)	398 (26%)
# cycles w/o fever or chills	1230 (87%)	1109 (74%)
# cycles w/headache, myalgias, arthralgia	67 (5%)	144 (10%)
# cycles w/o headache, myalgia, arthralgia	1325 (95%)	1379 (90%)

Hypotension

There were 79 reports of hypotension in 52 of the 143 patients (36%). There were 30 patients who had hypotension classified as a component of a hypersensitivity-type reaction, 2 patients who had hypotension as a component of VLS, and 19 patients in whom hypotension was attributed to both hypersensitivity-type reactions and to VLS (a listing of these 19 patients is contained in the Appendix, (Table A4). Hypotension was identified as a component of a hypersensitivity-type reaction (infusion-related reactions) when it occurred during or within hours of. Sixteen (33%) of the 49 patients who experienced hypotension as a manifestation of hypersensitivity-type reaction had hypotension as the sole symptom. Hypotension was identified as a component of VLS only if it occurred in conjunction with hypoalbuminemia and/or edema.

Edema

There were 120 episodes of edema reported in 47% (67/143) of patients. Edema was identified as a component of VLS in 30 of the 67 patients with edema. Multiple episodes of edema were reported in 10 of the 143 study patients (7%). In addition, multiple reports of different subtypes of edema (e.g., peripheral, periorbital, facial, pulmonary) were reported in 10 patients at a single timepoint.

Thromboembolic Events

Among 257 patients, there were 1 1 patients with thromboembolic events. These included superficial thrombophlebitis in six patients, 2 patients with uncomplicated deep venous thrombosis (DVT) and one patient with DVT complicated by a pulmonary embolism.

Cardiac:

Cardiac adverse events occurred in 19/1 43 (13%) of patients; a detailed listing of these events is provided in the Appendix A, Table 5A. While the majority of these events were reports of grade 1 tachycardia, there were three patients with grade 3-4 arrhythmias (two of these recorded as

atria1 fibrillation), 2 patients who suffered myocardial infarctions (one of whom died during a surgical procedure two weeks later) and one patient who suffered a fatal cardiac arrest; one of these events were fatal. The latter three events occurred approximately 2-4 weeks after therapy, however each of these subjects had persistent treatment-related symptoms which may have been precipitating factors (Patients #3 19, #2301, and #2601 enrolled in Protocol 93-04-10).

Renal:
Elevation of creatinine was noted in 7% (10 of 143) of patients. One patient in protocol 93-04-14 discontinued therapy due to other toxicities with a mild (< 3 x normal) elevation in creatinine; serum creatinine decreased after discontinuation of therapy.

Other Clinical Adverse events:
Other adverse events included 11 of 143 patients (8%) with reports of altered mental status and one episode of pancreatitis (1/143). Given the relatively high incidence of abdominal pain, nausea, vomiting! and diarrhea on these studies, consideration of more careful monitoring is warranted to evaluate for "subclinical" pancreatitis.

Laboratory abnormalities
The most common laboratory abnormalities (both overall and of a severe nature) were hypoalbuminemia (83%) and elevated transaminases (61%). Anemia, thrombocytopenia. and lymphopenia were reported in <10% of patients in the major efficacy studies. Grade 3-4 lymphopenia occurred in 48 of 143 (34%) patients. The time to resolution of lymphopenia, where this can be ascertained, has been protracted. Severe anemia (6 % Gr 3; 1% Gr 4) and severe thrombocytopenia (1 % Gr 3; 1 % Gr 4) were also observed but were not common..

Adverse reactions from all clinical studies are tabulated (Table 32); data from the combination of Protocols 93-04-l 0 and 92-04-o 1 are derived from the clinical investigator reports and sponsors' review of CRFs and laboratory data. Adverse events from Protocols 93-04-l 1 and 93-04- 14 are derived from individual investigator assessments.

TABLE 32: Adverse Events by Protocol In CTCL Patients (≥ 5% Incidence)

System	92-04-01/93-04-10 (n=143)		93-04-11 (N = 73) *		93-04-14 (N = 40)*	
	Any	Gr 3-4	Any	Gr 3-4	Any	Gr 3-4
Generalized						
Chills / fever	81 %	22 %	NA	NA	NA	NA
Fever	67 %	15 %	49 %	13 %	35 %	7 %
Asthenia	66 %	22 %	60 %	22 %	45 %	20 %
Chills	50 %	13 %	48 %	14 %	42 %	10 %
Anorexia	36 %	8 %	22 %	3 %	19 %	7 %
Weight decrease	14 %	4 %	NA	NA	NA	NA
Sweat	10 %	1 %	10 %	0	10 %	0
Dehydration	9 %	7 %	6 %	4 %	8 %	5 %
Insomnia	9 %	3 %	10 %	6 %	8 %	3 %
Flu-like syndrome	8 %	0	NA	NA	NA	NA
Somnolence			11 %	3 %	7 %	0
Nervous System						
Pain	48 %	13 %	22 %	4 %	20 %	8 %
Headache	26 %	3 %	32 %	6 %	38 %	10 %
Dizziness	22 %	1 %	22 %	6 %	10 %	3 %
Paresthesia	13 %	1 %	8 %	3 %	5 %	3 %
Nervousness	11 %	1 %	10 %	1 %	8 %	0
Confusion	8 %	6 %	NA	NA	NA	NA
Cardiovascular						
Edema	47 %	15 %	7 %	4 %	13 %	0
Hypotension	36 %	8 %	14 %	6 %	8 %	3 %
Chest Pain	24 %	6 %	11 %	1 %	5 %	5 %
Periph.Edema	24 %	4 %	19 %	4 %	25 %	8 %
Vasodilatation	22 %	1 %	16 %	4 %	13 %	3 %
Tachycardia	12 %	1 %	4 %	0 %	13 %	3 %
Chest Tightness	11 %	1 %	10 %	1 %	5 %	0
Thrombosis	7 %	4 %	NA	NA	NA	NA
Arrhythmia	6 %	3 %	NA	NA	NA	NA
Hypertension	6 %	0	6 %	3 %	5 %	0
Respiratory						
Dyspnea	29 %	14 %	21 %	10 %	25 %	13 %
Cough Increase	26 %	2 %	19 %	4 %	28 %	3 %
Lung Disorder	8 %	0	NA	NA	NA	NA
Pneumonia	7 %	6 %			5 %	3 %
Asthma			7 %	4 %	10 %	0
Gastrointestinal						
Nausea / vomiting	64 %	14 %	NA	NA	NA	NA
Nausea	55 %	11 %	50 %	16 %	50 %	10 %
Vomiting	34 %	9 %	21 %	8 %	20 %	8 %
Diarrhea	29 %	3 %	21 %	4 %	25 %	5 %
Constipation	9 %	1 %	8 %	1 %	10 %	0
Abdominal pain	12 %	3 %	11 %	7 %	13 %	3 %
Dyspepsia	7 %	0	NA	NA	NA	NA
Dysphagia	6 %	1 %	7 %	1 %	8 %	8 %
Infectious Disease						
Infection	48 %	24 %	18 %	4 %	35 %	13 %
Rhinitis	13 %	1 %	15 %	3 %	25 %	8 %
Pharyngitis	17 %	0	19 %	3 %	23 %	3 %
Upper Resp. Infect.	11 %	0	23 %	1 %	23 %	8 %

System	Adverse Events by Protocol in CTCL Patients					
	92-04-01 & 93-04-10 (N = 143)		93-04-11 (N = 73)*		93-04-14 (N = 40)*	
	Any	Grade 3-4	Any	Gr 3-4	Any	Gr 3-4
Infectious Disease						
Sinusitis	7%	1 %	7%	0	3 %	0
Sepsis	8%	7 %	1 %	1 %	3%	3 %
Conjunctivitis	8 %	1 %	6 %	0	15 %	5 %
Urin Tract Infection	9 %	4 %	6 %	3 %	3 %	3 %
Dermatological						
Rash	34%	13 %	33%	7 %	33 %	23 %
Pruritus	20 %	3 %	7 %	3 %	15 %	8 %
Injection Site Rx	8 %	1 %	7 %	1 %	3 %	0
Facial edema	13%	4 %	8 %	1 %	8 %	3 %
Rash, maculopap.	13%	4 %	1 %	0	10 %	0
Heroes simplex	6 %	1 %	1 %	0	10 %	3 %
Acne			6 %	0	5 %	0
Contact dermatitis			7 %	4 %	5 %	3 %
Urticaria			6 %	3 %	8 %	0
Musculoskeletal						
Myalgia	18 %	2 %	27 %	10 %	15 %	0 %
Back Pain	22 %	5 %	21 %	8 %	18 %	8 %
Arthralgia	8 %	1 %	11 %	8 %	20 %	3 %
Laboratory Studies						
Hematology						
Anemia	18 %	6 %	3 %	1 %	3 %	3 %
Thrombocytopenia	8 %	2 %				
Leukopenia	6 %	3 %				
Leukocytosis					5 %	3 %
Renal / Electrolytes						
Creatinine increase	7 %	1 %	1 %	0	8 %	0
Hypokalemia	6 %	0	4 %	0	3 %	0
Urinalysis						
Hematuria	10 %	3 %	4 %	1 %	5 %	3 %
Albuminuria	10 %	1 %	1 %	0	5 %	3 %
Pyuria	10 %	1 %	3 %	1 %	10 %	3 %
Hepatic / Metabolic						
Hypoalbuminemia	83 %	14 %	7 %	6 %	10 %	5 %
↑Transaminase	61 %	15 %	14 %	8 %	15 %	8 %
Hypocakemia	17 %	3 %	1 %	0		
Hyperglycemia			1 %	0	5 %	3 %

* Data from Protocols 93-04-I l and 93-04-14 are placebo-controlled studies (blind unbroken for AEs) and reports derived from investigator's assessment (data not verified by sponsor).

Discontinuation of study drug due to Adverse Events

A total of 93 of the 143 patients did not complete all planned therapy. Among these 94 patients, 42 (45%) were identified as discontinuing treatment due to disease progression, 38 (40%)

withdrew due to adverse events, 8 (10%) patients withdrew at their own request and the remainder for a variety of reasons (worsening symptoms, protocol violation, death, and "unspecified". The adverse events that were associated with treatment discontinuation in these studies were: flu-like symptoms in 11 patients (8%); respiratory symptoms in 8 patients (6%); vascular leak syndrome in 8 patients (5%); fatigue and/or anorexia in 5 patients; and atrial fibrillation, hypersensitivity reaction, exacerbation of BCNU-related pulmonary toxicity, anemia, eosinophilia, and decreased performance status (1 patient each).

Serious Adverse Events

Serious adverse events were defined as events which resulted in any of the following: death; an immediately life-threatening situation; hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity; congenital anomaly; new diagnosis of cancer; or overdose. There were a total of 173 serious adverse events (SAEs) reported in 86 of the 256 patients enrolled in the lymphoma trials. One hundred twenty-five SAEs were reported in 63 patients (44%) of the 143 patients enrolled in Protocols 92-04-01 and 93-04-10. There were also 27 SAEs reported in 15 of the 73 patients enrolled in Protocol 93-04-11 and 21 SAEs reported in 8 (20%) of the 40 patients enrolled in Protocol 93-04-14. There was not a clear dose-response relationship with regard to the incidence of SAEs, i.e., increased incidence of SAEs at higher doses (≥18 μg/kg/d). however, there was a higher proportion of patients who discontinued treatment for adverse events in the 18 μg/kg/d arm as compared to the 9 μg/kg/d arm in Protocol 93-04-10 (42% vs. 31%, respectively) and a higher incidence of grade 3 and 4 adverse events (58% vs. 49%, respectively).

In the major efficacy studies, the most common serious adverse event was infection, which was reported in 25 (17%)of 143 patientsThe incidence of infection was higher in patients with more extensive cutaneous involvement. The reasons for this were not clear from these studies, however potential reasons include greater disruption of integrity of the skin, greater extent of prior therapy which may have immunosuppressive effects of prolonged duration, and greater use of central venous access catheters for drug delivery. In addition, 10 of the 25 patients with infection had multiple (more than one) episode of infection. Serious infectious events included sepsis, pneumonia, endocarditis, pneumonia, staphylococcal infection, sinusitis, urinary tract infection, and Herpes zoster.

Other serious adverse events included drug-induced fever that led to hospitalization in 6 patients (4%), hypotension (3%), rash and maculopapular rash (3%), pulmonary edema (1%) and dehydration (1%).

There were 17 reports of second malignancies among 8 patients. The majority of these were squamous cell and basal cell cancers of the skin, however there were also one report each of prostate cancer and anaplastic astrocytoma. The sponsor has rated these events as unrelated to the study drug. Given the age of the patient population studied and the extent of prior carcinogenic therapies, the incidence of malignancies does not seem to be excessive.

Deaths on Study (within 90 days of last dose)

Protocol 92-04-O 1

1. Patient 102: A 60 yr old male with stage III CTCL enrolled into the 6 µg/kg/d dose level cohort. The patient suffered a DVT on day 12 of cycle 1 and discontinued treatment for this adverse event. The patient died of progressive CTCL on day 45, 40 days after the last dose.
2. Patient 402: A 27 year old male with HD, who was enrolled 3 months after autologous bone marrow transplantation, with a history of possible pulmonary toxicity following transplant possibly related to the myeloablative regimen. The patient was enrolled in the 9 µg/kg dose level cohort. The patient developed fever and infiltrates with onset of dyspnea 4 days later and progressive ARDS. At autopsy, diffuse alveolitis and inflammatory infiltrate was reported; there was no identification of an infectious organism or of involvement with Hodgkin's disease. The patient died on day 22 of cycle 2, 17 days after the last dose of study drug. The death was rated by the investigator as possibly related to DAB-IL2.
3. Patient 103 died on study day 15, 10 days after the last dose. This subject was diagnosed with a grade 2 central venous catheter infection (*S. aureus*) and a CMV infection on day 7, complicated by DIC, dyspnea, thrombocytopenia, hyperbilirubinemia and hypoalbuminemia
4. Patient 704 with Hodgkin's disease (#704) died 49 days after the last dose due to progressive disease. This patient was hospitalized for pain control due to malignant involvement of the spine, which was reported as a serious adverse event.

Protocol 93-04- 10

1. Pt 2601 was a 68 year old male with stage IIa CTCL and a history of CAD (S/P CABG) and thoracic aortic aneurysm. On day 15 of cycle 1, the patient reported angina. On day 27 of cycle 1 he was diagnosed with septic arthritis. On day 3 1 of cycle 1, 26 days after the last dose of study drug. he suffered a fatal myocardial infarction during a surgical procedure to repair a pseudoaneurysm of the left groin.
2. Pt. 2301 was a 71-year-old male with stage Ib CTCL randomized to 18 µg/kg/d, who died on day 30 of the sixth cycle, 25 days after the last dose of study drug. The patient had experienced toxicity during cycle 1 (dehydration and delirium on day 3, cycle 1) and on study day 23 of cycle 6, while living in a nursing home facility, he was reported to have dehydration, disorientation, leg contractures, and a 25 lb. weight loss. The patient died seven days later.
3. Patient 1101 was a 75 year old female with stage Ib CTCL, as well as a medical history significant for anemia, herpes simplex virus infection, para-psoriasis, and recurrent urinary tract infections. This patient, enrolled at the 18 µg/kg/d level, was discontinued from the study on cycle 2 day 40 for "low-grade" disseminated intravascular coagulation, with deep venous thrombosis. The patient died on cycle 2 day 89 due to staphylococcal sepsis and respiratory failure. Autopsy findings were consistent with sepsis and congestive heart failure.
4. Pt 1102 was an 84 year old female with stage IIa CTCL and a history of pulmonary hypertension, randomized to 9 µg/kg/d. She received one cycle of therapy and was discontinued for hypoalbuminemia (persistent toxicity?) on study day 22. She was reported

to have bacteremia a week later (study day 29). The patient died 66 days after the last dose of study drug. No cause of death has been provided.

5. Pt. 319 was a 76 year old female with stage IIb CTCL and a history of non-insulin-dependent diabetes, hypothyroidism and hypertension that was randomized to 18 μg/kg/d. The patient discontinued treatment due to toxicity (vascular leak syndrome) after cycle 2. Toxicities included vascular leak syndrome during cycle 2, bacteremia on study day 8 of cycle 2, pulmonary embolus on day 10 of cycle 2, and a myocardial infarction, in association with hypoalbuminemia on day 23 of cycle 2. The patient died 60 days after the last dose of study drug. The cause of death was infection.
6. Pt 2119 was a subject who has been identified by the sponsor as ineligible for the protocol; the sponsor has excluded the patient from database for safety and efficacy. This subject died of acute renal failure.

Protocol 93-04-11

1. Pt 2453 is a 60 year old male with stage Ia CTCL who received 7 cycles of therapy (blind has not been broken). The patient was diagnosed with anaplastic astrocytoma during cycle 7 of treatment and died on day 82 of cycle 7, 77 days after the last dose of study drug.

B. Integrated Safety Information in Patients without Malignancy

(1) Description of Protocols:

Table 33 summarizes the trial designs of protocols that are evaluating $DAB_{389}IL2$ in non-malignant conditions; there were a total of 12 studies. Protocol 93-04-12 was developed to characterize the pharmacokinetic (PK), tolerability and safety of citrate-buffered formulation $DAB_{389}IL2$ to that of the ——— buffered formulation $DAB_{389}IL2$. Protocol 93-04-06 was designed to evaluate the activity, safety and tolerability of $DAB_{389}IL2$ vs. placebo in recent-onset ——————————— Protocol 92-04-04 was designed to explore the activity of $DAB_{389}IL2$ based on ——— and ——————— end-points, pharmacokinetics, safety and tolerability in ——————— patients. There are 4 protocols designed to evaluate the activity of $DAB_{389}IL2$ in psoriasis (2 of which are ongoing at the time of this review) and 5 protocols, which evaluated activity in ——————————

TABLE 33 : Clinical Trials in Non-malignant Conditions

Protocol	Population	Status	N	Design	Treatment Plan	# Courses
93-04-12	Healthy	complete	45	Double-blind	6 µg/kg/d qd x 5	1
93-04-06	[redacted]	complete	18	Double-blind; placebo-control	placebo vs. 1 vs. 2.5 µg/kg/d qd x 5	1
94-04-09	[redacted]	complete	24	Open-label; dose-escalation	2, 4, 6, or 9 µg/kg/d daily x 5 for 4 wks	≤ 6
94-04-16		complete	41	Double-blind; placebo-control	0, 5, 10, or 15 µg/kg/d d 1-3 weekly x 4	1
96-04-19*		ongoing	32	Open-label; dose escalation	0.5 vs. 1.5 vs. 5 µg/kg/d qd x 3 every 2 wks x 4	1
96-04-21		ongoing	1	Open-label	5 µg/kg/d qd x 3 every 2wk x 4, or q2 wks x 4	1
92-04-02	[redacted]	complete	55	Double-blind; placebo-control; with cross-over to 3 µg/kg/d▲	0, 1.5, 3, or 6 µg/kg/d daily x 5 q 4wk	2
92-04-03	[redacted]	complete	43	Open-label; prior IL-2 fusion protein	3 µg/kg/d qd x 5 q 4wk, or at flare	≤ 8 cycles / 2 years
92-04-05		complete	20	Open-label; combination with methotrexate	or 3 µg/kg/d daily x 5	1
95-04-18		ongoing	4	Open-label; prior IL-2 fusion protein	3 µg/kg/d daily x 5 every 28day or flare	≤ 2 years
92-04-04	[redacted]	complete	24	Open-label; dose-escalation	1 vs. 2.5 vs. 4 µg/kg/d daily x 5 q 28 days	3
94-04-15	[redacted]	complete	1	Single pt study	15µg/kg/d qd x 5	1

* No further data available for 1 patient in Protocol 96-04-19

▲ 11 patients crossed-over from placebo to active at a dose of 3 µg/kg/d

Demographics:

Table 34 summarizes the baseline entry characteristics for patients according to underlying disease. Ninety-four percent (289 of 307 patients) of the patients were less than 65 years of age. The patient populations with the youngest median age were those with [redacted] (age 24 years) and normal volunteers (age 33 years). The patient populations also differed from each other in the proportion of women (fewer women enrolled, except for studies conducted in [redacted] and in ethnic representation.

TABLE 34: Baseline Entry Characteristics for Studies in Non-malignant Conditions

Parameter		[redacted] N = 97	[redacted] N = 122	[redacted] N = 25	[redacted] N = 18	Healthy N = 45	All N = 307
Age (year)	range	20 - 80	25 - 75	24 - 48	13 - 33	19 - 63	13 - 80
	> 65 years	9 (9 %)	9 (7 %)	0 (0 %)	0 (0 %)	0 (0 %)	18 (6 %)
Sex	Male	55 (57 %)	31 (25%)	23 (92 %)	13 (72 %)	43 (96 %)	165 (54 %)
	Female	42 (43 %)	91 (75%)	2 (8 %)	5 (28 %)	2 (4 %)	142 (46 %)
Race	White	66 (68 %)	4 (3 %)	14 (56 %)	18 (100 %)	33 (73 %)	135 (44 %)
	Black	4 (4 %)	0 (0 %)	9 (36 %)	0 (0 %)	11 (24 %)	24 (8 %)
	Other	3 (3 %)	0 (0 %)	2 (8 %)	0 (0 %)	1 (2 %)	6 (2 %)
	N/A	24 (25 %)	118 (97 %)	0 (0 %)	0 (0 %)	0 (0 %)	142 (46 %)

Safety summaries:

Protocol 93-04-l 2 (Normal volunteers)

Forty of 45 patients (89%) reported adverse events. The most frequent clinical AE's, were, in decreasing order of incidence, rash 29 % (Gr. 3-4 in 2 pts), headache 29% (Gr. 3-4 in 1 pt), chills/fever 24% (Gr. 3-4 in 3 pts), asthenia 22% (Gr. 3-4 in 0), myalgia 20% (Gr. 3-4 in 0), nausea 18% (Gr. 3-4 in 2 pts), dizziness 13% (Gr. 3-4 in 1 pt),and pain at the injection site 16%. Laboratory abnormalities included: transaminase elevations - 7 1 %, transient increase in neutrophils (incidence not provided) and concurrent decrease lymphocytes (incidence not provided). The severity grade for laboratory abnormalities was not provided in the application. There was one report of a serious adverse event, patient # 264 (see SAE's below) who reported Gr. 3-4 chest pain.

Protocol 93-04-06 [redacted]

Data were provided for 18 patients who included 6 patients who received placebo and 12 patients who received $DAB_{389}IL\text{-}2$. Adverse events were reported in 13 patients (72%); all 6 patients receiving placebo reported adverse events, in comparison to 7 of 12 patients (58%) who received $DAB_{389}IL\text{-}2$ therapy . Chills and fever were the most frequent events. reported in 17% (1 placebo and 2 $DAB_{389}IL\text{-}2$ patients; Gr. 3-4 in 1 pt). Other adverse events reported in l-2 patients each were headache, fungal infection. laryngitis and abdominal pain. Adverse events reported only in patients receiving placebo were diarrhea (33%). esophageal ulcer (17%). myalgia (17%). and rash (17%). Laboratory abnormalities observed in $DAB_{389}IL\text{-}2$ patients consisted of a 33% (4 of12) incidence of Gr.2 - 3 events, which were increased creatinine, hyperbilirubinemia, and anemia, all of which fully resolved. There were no reports of transaminase elevations. No laboratory abnormalities were observed in placebo patients. There were no reports of serious adverse events in this study.

Protocol 94-04-09 [redacted]

Safety data were provided for 24 patients. The most frequent clinical adverse events were fever and/or chills in 75% of patients (n=18), which was of moderate to severe toxicity in one patient. The frequency of fever and/or chills appeared to be dose-related, reported in 50% of patients at

the 2 μg/kg/day does and 100% at 9 μg/kg/d. Other common adverse events were: headache (46%), asthenia (42%), dizziness (42%), nausea and/or vomiting (42%), arthralgia (38%), pruritus (29%), unspecified pain (25%), and pharyngitis (25%). Adverse events which were of grade 2-3 in severity include arthralgia (16%), asthenia (12%), pain, NOS (1 2%) and pruritus (8%).

The most frequent laboratory abnormalities reported were LFT elevations (29%), decreased hemoglobin (25%), and hypoalbuminemia (17%). One patient (treated at 4 μg/kg/day) had transaminase levels five times the upper limits of normal, There were intermittent abnormal urinalysis finding (RBC, WBC or albumin) in 15 of 24 pts; one patient who was dehydrated had an elevated creatinine.

There was one reported serious adverse event (sepsis, at 2 μg/kg/day). Five patients discontinued therapy due to adverse events. Three patients had hypersensitivity-like reactions; this includes on patient who discontinued treatment due to a maculopapular rash and two patients who reported dyspnea.

Protocol 94-04- 16 [illegible]

Safety data was provided for 29 patients who received $DAB_{389}IL\text{-}2$. Moderate to severe adverse events, included (in order of decreasing incidence) fever and/or chills, pruritus, myalgias, asthenia, emesis, and hypotension. The most frequent clinical adverse events were: chills and/or fever in 76% (moderate to severe in 13 of 22 patients), asthenia in 45% (mod. to severe in 7 of 13 patients), headache in 38% (mod. to severe in 5 of 11 patients), myalgia in 38% (mod. to severe in 8 of 11 patient), pruritus in 38% (mod. to severe in 9 of 11 patients), and nausea/vomiting in 34% (mod. to severe in 5 of 10 patient). Other commonly reported events were vasodilatation in 24 (mod. to severe in 4 of 7 patients), edema in 17% (mod. to severe in 3 of 5 patients), somnolence in 17% (mod. to severe in 1 of 5 patients) and hypotension in 17% (mod. to severe in 4 of 5 patients). There were 4 reports of infection (14%) with on moderate/severe event and 3 events of hypersensitivity. The most frequent laboratory AE's reported were increased transaminases and decreases in albumin; these returned to baseline by the end of dosing.

Ten patients discontinued study drug due to adverse events (see below); 3 patients experienced serious adverse events leading to hospitalization (see below).

Protocol 96-04-l 9 [illegible]

Safety information was provided on 32 patients. The majority of clinical adverse events were mild or moderate in severity; there was one patient each with a severe or serious adverse event. The most common adverse events were: nausea (20%), asthenia (20%), arthralgia (10%), pain (10%), chills (1 0%), hypotension (1 0%), anorexia(10%), diarrhea (1 0%), lymphadenopathy (1 0%), and taste perversion (10%). Two patients experienced transiently increased liver enzymes during the first cycle in both instances.

One patient developed Gr. 4 leukopenia. One patient was reported with renal calculi (Grade 3 clinical event) and one patient (pt # 306) suffered a cellulitis, which required hospitalization and led to discontinuation of therapy.

Protocol 96-04-2 1 ———)
No information was provided for this single patient trial.

Protocol 92-04-02 (--———————
Safety information was provided for 55 patients. The most frequently reported adverse events were: fever 33% (moderate in 2 of 14), nausea 33% (moderate in 5 of 14), pruritus 26% (moderate in 3 of 1 1), rash 26% (moderate in 3 of 1 1), chills 21%, diarrhea 19%, and dyspepsia 10%. Five patients had serious adverse events necessitating hospitalization; all of these events subsequently resolved. Two patients discontinued treatment due to adverse events.

Protocol 92-04-03 (———————)
Safety information was submitted for 43 patients. The most frequent clinical adverse events, in order of decreasing incidence, were: nausea and vomiting 42% (moderate severity in 1 of 18 patients), rash 28% (moderate severity in 2 of 12 patients), chills and fever 26% (moderate severity in 1 of the 1 1), infection 23% (moderate severity in 1 of 10 patients); asthenia 21% (moderate severity in 3 of 9 patients), diarrhea 19%(moderate severity in 1 of 8 patients), and pain (19%; moderate severity in 2 of 8 patients). The most common laboratory abnormality was transaminase elevation, reported in two patients. One of the two patients discontinued therapy due to Gr. 2 transaminitis after Cycle 1, resolving one week later. There were no urinary system abnormalities were observed.

Protocol 92-04-05 (- ———————)
Safety information was provided on 20 patients. Three patients (15%) reported a total of 41 adverse events. The majority (71 %) were mild in severity and the remaining 29% were of moderate severity. The most frequently reported adverse events were chills and fever (15%) infections (15%), mild-to-moderate nausea and vomiting (15%), and injection site reactions (10%). Eight patients (40%) experienced hypoalbuminemia, 4 patients experienced increased transaminases, and 2 patients developed pyuria (one grade 2 and one grade 3 event). Pyuria resolved within one week.

Protocol 95-04-l 8 (———————
Safety data was provided on 4 patients. All patients reported at least one clinical adverse event of mild severity; there were no moderate or severe clinical adverse events. Arthralgia was reported in 4 of 4 patient, nausea in 3 patients, and myalgia in 2 patients. One patient each reported asthenia, chills, injection site reaction, pain (unspecified), diarrhea, paresthesia, and somnolence. One patient (# 23 10) had experienced a serious adverse event (surgery for metatarsal resection). No patients discontinued study drug due to adverse events.

Protocol 92-04-04 ———————)

Safety information was submitted for 24 patients. Twenty-two (92%) of patients (22 of 24 pts) reported one or more adverse events. Among the 130 adverse events, 90 (69 %) were graded as mild in severity, 34 (26 %) were moderate, and 6 (5%) were severe. Elevated liver function tests were the most frequently reported event. There were 4 patients with LFT's reported to be 2 time the upper limits of normal (2 x ULN), 2 patients in whom LFT's were elevated to 3 x ULN, 2 patients in whom LFT's were 4 x ULN, and one patient in whom LFT's were 10 x ULN (the latter patient had a concurrent hepatitis C infection). All elevations except one (the latter patient) resolved within the 16 day observation period.

Protocol 94-04-l 5 ([redacted] ,
The one enrolled patient received 15 µg/kg/d x 4 daily doses and was observed for 2 weeks. The patient had Gr. III hematuria, confusion, and nausea; Gr. II fever, weight loss, hypokalemia, hyponatremia, hypocalcemia, increased transaminase, proteinuria, decrease in serum protein, and Gr. I tachycardia and urinary retention. This patient died due to disease progression 41 days after last dose.

Adverse events leading to termination of DAB389IL2:
The rate of withdrawal from study from study& to adverse events was highest among patients with psoriasis (9%-3 1 %) but was similar among the normal volunteers, patients with [redacted] - - . o r [redacted] patients (O-7%). A description of the adverse events leading to discontinuation of treatment is provided. by study, below:

Protocol 93-04- 12 (normal volunteers): incidence 7 % (3 of 45)
- Pt 225: Grade II generalized erythematous maculopapular rash, occurring after the 4th dose; treated with oral antihistamines and topical corticosteroids.
- Pt 286: Gr. III chills with rigors (persisting for 2 hours, and treated with acetaminophen), Gr. III nausea, and transient (30 minutes) orthostatic hypotension with dizziness occurring one hour after completion of therapy.
- Pt. 264 (--buffered formulation): Past medical history significant for smoking and a parent with ischemic cardiac disease. The patient complained of chest pain (pleuritic in nature) with dyspnea, radiation to the left arm, worse on inhalation and lying on the left side. Cardiac evaluation was negative (EKG, chest X-ray, cardiac enzymes, echocardiograms and coronary angiography). There was complete resolution of symptoms over 3 days.

Protocol 93-04-06 ([redacted] : 0 % (0 of 18)

94-04-09 ([redacted] incidence2 1 % (5 of 24) in Volume 87
- Pt 003: Past medical history significant for psoriatic arthritis. This patient discontinued therapy after 9 cycles due to moderately severe arthralgia, first reported during cycle 8 and persisting through cycle 9. Treatment of this patient continued in violation of the protocol with continued and escalated treatment despite psoriasis flare during cycles 4 and 5.
- Pt 004: Past medical history significant for > 70% body surface area involvement of

psoriasis. This patient discontinued treatment after cycle 1 due to *S. aureus* bacteremia attributed to the indwelling venous catheter.

- Pt 019: This patient discontinued therapy after the 2nd infusion (day 2) of cycle 2 due to low back pain and a report of feeling flushed (vasodilatation). The vasodilatation resolved within one day.
- Pt 023: Past medical history significant for treated hyperthyroidism. This patient discontinued therapy due to recurrent hyperthyroidism on cycle 1 day15.
- Pt 024: This patient discontinued therapy due to development of a maculopapular rash on cycle 1 day 9.

Protocol 94-04-16 (——— : incidence 31 % (10 of 32) in Volume 84

- Pt 1011: Past medical history significant for chronic ethanol abuse. The patient received 4 doses of therapy on study days 1, 2, 3, and 8.The patient discontinued treatment on study day 10 due to arterial and venous thromboses (bilateral occlusion of anterior and posterior tibial arteries, treated with femoral stents, heparin, and TPA). This patient was later determined to have a profile consistent with a hypercoaguable, i.e., elevated plaminogen activator inhibitor, elevated antiplasmin, and anti-phospholipid antibodies. Eleven months after the later (day 355), the patient underwent amputation of the left great toe.
- Pt 1010: This patient discontinued treatment after completing the 6th dose on day 10 due to rash (exfoliative erythroderma) and experienced asthmatic bronchitis on study day 33
- Pt 6003: This patient discontinued treatment after receiving 3 doses, on day 9 due to pruritic rash (eruptive and macular).
- Pt 1004: This patient discontinued treatment on study day 10, after six doses, due to persistent nausea. Nausea was first noted on study day 1 and did not resolved until day 17.
- Pt 1007: This patient discontinued treatment on day 15 due to rash (maculopapular; urticarial) and exfoliative dermatitis.
- Pt 2001: This patient discontinued treatment after 2 doses, on study day 3 due to hypotension (90/60) associated with a near-syncopal episode.
- Pt 1003: This patient discontinued treatment after 2 doses on study day 3 due to fever, chills, asthenia.
- Pt 3004: This patient discontinued treatment after receiving 2 doses, on day 8 due to orthostatic hypotension. The onset of this event was study day 3; symptoms resolved by study day 11.
- Pt 5011: This patient discontinued treatment on day 9 due to facial edema, occurring from day 7 to day 15.
- Pt 6005: This patient discontinued treatment, after receiving 3 doses, on day 5 due to rash (erythematosis) and worsening of psoriasis.

Protocol 96-04-19 (1 ~~~): incidence 9% (3 of 32)

- Pt 306: This patient discontinued treatment after receiving 9 doses, due to left lower leg cellulitis, which necessitated hospitalization.
- Pt 504: This patient discontinued treatment due to facial edema.

- Pt 602: This patient discontinued treatment due to moderate generalized pruritic, papular, edematous rash.

Protocol 96-04-21 ( ): no information provided

Protocol 92-04-02 ( ): incidence 7% (4 of 55) in Volume 97

- Pt 101: This patient discontinued treatment due to rash on day 17
- Pt 211: This patient discontinued treatment due to mild facial edema and moderate nausea on day 7.
- Pt 302: This patient discontinued treatment due to vasovagal syncopal episode with severe hypotension.
- Pt 505: This patient discontinued treatment due to rash on day 9

Protocol 92-04-03 ( ): incidence 7% (3 of 43)

- Pt 303: This patient discontinued treatment on C1D97 due to pericarditis. Although this is a known complication of the sponsor attributed this event to the treatment. Additional AE's occurring during treatment were nausea, hives, papules, pruritus, and hypertension.
- Pt 309: This patient discontinued treatment due to hives which developed 5 minutes after completing 1st infusion (C1D1). The hives recurred, and were more extensive, despite pre- and post-medication with diphenhydramine. The rash resolved on C1D13.
- Pt 707: Past medical history significant for transaminitis of unknown etiology. The patient discontinued treatment due to a Gr. 2 elevation of ALT and AST, one week after completing Cycle 1.

Protocol 92-04-05 ( ): incidence 5% (1 of 20), Volume 92

- Pt 108: This patient discontinued therapy due development of of the right antecubital fossa after 3 consecutive daily doses of study drug.

Protocol 95-04-18 ( ): incidence 0% (0 of 4)

Protocol 92-04-04 ( ): incidence 4% (1 of 25)

- Pt. 303: This patient discontinued treatment due to severe elevation of hepatic transaminase (ALT, AST, and LDH) levels, occurring one week after 1st dose of therapy, and continuing to rise over the next 4 weeks. The transaminitis was associated with an increase in alkaline phosphatase (3x normal) and an increase serum bilirubin levels (2x normal). The patient was shown to be hepatitis C antibody positive, but asymptomatic. Liver biopsy demonstrated chronic hepatitis with superimposed acute viral hepatitis. All liver enzymes returned to normal. The patient was discontinued from the study after cycle 1.

Protocol 94-04-15 (: incidence 100% (1 of 1)

- The only patient enrolled received 15 μg/kg/d x 4 daily doses followed by 2 weeks

observation. The patient developed Gr. 3 hematuria, confusion, and nausea; Gr. 2 fever, weight loss, hypokalemia, hyponatremia, hypocalcemia, increased transaminase, proteinuria, decrease in serum protein, and Gr. 1 tachycardia and urinary retention. This patient died due to disease progression 41 days after last dose.

VIII. REVIEWER COMMENTS

Protocols 92-04-01 and 93-04-10 have shown a 30-40% objective clinical response rate in patients with previously treatedcutaneous T-cell lymphoma. Responses were observed both in patients with advanced ($\geq$ IIb) and those with early ($\leq$ IIa) stage disease. The complete response rate in the primary efficacy study (93-04-10), as assessed by an independent review panel, was 10%. The response rates and the durability of the complete and partial responses in these trial suggest that a clinical benefit may be derived. The data in these two trials are supported by objective anti-tumor responses observed in ongoing studies and in other types of non-Hodgkin's lymphoma.

There was no clear evidence that objective clinical responses correlated with relief of tumor-related symptoms, particularly pruritus. In patients who achieved a complete pathological or clinical response, all patients had complete resolution of symptoms of pruritus, however use of rescue medications for treatment of these symptoms was continued in all but one patient. This suggests incomplete relief of symptoms by $DAB_{389}IL\text{-}2$ alone. In patients who achieved partial responses, there was no clear evidence that symptomatic improvement was achieved nor were rescue medications consistently reduced in use.

There was no evidence of a dose-response relationship in the clinical studies and the optimal duration of treatment has not been established. Furthermore, the product is highly immunogenic and the pharmacokinetic properties are significantly altered by the immune response. Further studies are needed to investigate the dose-response relationship and optimal duration of treatment.

The proposed mechanism of action requires binding to the IL-2 receptor and uptake into the cell. The IL-2 receptor exists in three forms of varying affinity, based upon the protein composition. Of the three possible protein components of the IL-2 receptor. only CD25 expression (which is present in both the low- and high-affinity, but not the intermediate-affinity IL-2 receptor) was documented in tumor specimens and was a condition of entry into the clinical studies. Thus, evidence of clinical benefit was established only in approximately 60% of patients with CD25-expressing CTCL. Since adverse events appear to be non-specific (not mediated by binding to CD25+ tumor binding) and clinical benefit has not been demonstrated in CD25 negative CTCL disease, denileukin diftitox should not be used in CD25 negative tumors outside of the setting of appropriate studies which are designed to verify the anti-tumor activity of denileukin diftitox. Commercial assays for detection of CD25 expression is in progress; until data are received which validate the comparability of the commercial assay to the experimental screening assay, a testing service, provided by the Seragen or a subcontractor of Seragen, is necessary to identify patients

for whom denileukin diftitox is indicated,

In addition, further investigation of the mechanism of action and appropriate patient population should be conducted. Specific areas to be addressed include: 1) determination of the minimum density of IL-2R expression or IL-2R number per cell which is required for anti-tumor activity, 2) determination of the specific IL-2R subtype present in CD25+ CTCL (low vs. high), 3) determination of the anti-tumor activity in tumors with low, intermediate and high-affinity IL-2R bearing tumors, and 4) determination of whether there is activity in CD25 negative CTCL (and if so, the potential mechanism of action in such patients).

Many of the toxicities observed with this product may result from either of the active components of the fusion protein. Known toxicities of IL-2 include capillary-leak syndrome, which is characterized by fluid retention, interstitial edema, hypoalbuminenia, hypotension, and pre-renal azotemia, which may progress to acute renal failure. Patients with a history of cardiovascular disease, cardiomyopathy or impaired pulmonary function are at increased risk for severe toxicity due to this syndrome. Other toxicities observed with systemic administration of IL-2 include hepatic toxicity with transaminitis and hyperbilirubinemia, a variety of adverse events involving the CNS (most commonly mental status changes), and exacerbation of or predisposition to the development of autoimmune endocrinopathies. Toxicities, which may arise through non-targeted uptake of the toxins that mediate protein-synthesis inhibition, such as diphtheria toxin, include capillary leak syndrome, rhabdomyolysis, and hepatic transaminitis.

The observation that the incidence of toxicities may decrease on second and subsequent cycles does not necessarily indicate that tachyphylaxis or tolerance has occurred. There was a high attrition rate in one of the two studies; thus a decrease in the incidence of toxicities may be due to a decrease in the proportion of less healthy patients (those who are more at risk for significant toxicity through co-morbid conditions or those with more advanced disease or progressive tumor). In addition. the rapid development of neutralizing antibodies in the virtually all patients after 2 cycles of treatment may also be contributing to a decreasing risk of toxicity by rapid clearance of the drug product. The sponsor has already stated that the incidence of transaminase elevations appears to be lower in patients with neutralizing antibodies. Results of the ongoing placebo-controlled trial may be useful in addressing some of these issues. Additional trials will be necessary to determine whether the use of prophylactic premedication is effective in ameliorating the toxicity of denileukin diftitox.